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Seini Matangi

(Typed or printed name of person mailing paper or fee)

Patent

Attorney's Docket No. 005699-379

**IN THE UNITED STATES PATENT AND TRADEMARK OFFICE**

In re Patent Application of )  
)  
KELLEHER, et al. )  
)  
Application No.: Unassigned ) Group Art Unit: Unassigned  
(Continuation of U.S. 09/500,650) )  
)  
Filed: February 9, 2000 ) Examiner: Unassigned  
)  
For:  $\alpha$ -ARYL-N-ALKYLNITRONES AND )  
PHARMACEUTICAL )  
COMPOSITIONS CONTAINING )  
SAME )

**PRELIMINARY AMENDMENT**

Assistant Commissioner for Patents  
Washington, D.C. 20231

Sir:

Prior to examination of the above-identified patent application on the merits, please amend the claims as follows:

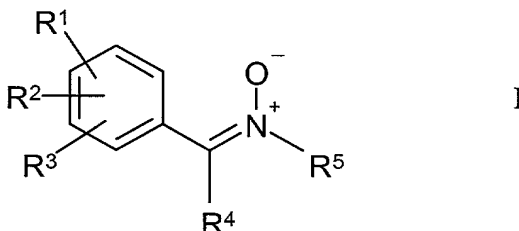
**In the Claims:**

Please cancel Claims 1-44, 49, and 53.

Please amend the remaining claims as follows:

45. A method for ameliorating a cause of a neurodegenerative disease in a patient at risk for developing the neurodegenerative disease which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically

acceptable carrier and an effective neurodegenerative disease-cause ameliorating amount of a compound of formula I:



wherein

R<sup>1</sup> is selected from the group consisting of alkoxy, alkaryloxy, alkycycloalkoxy, aryloxy, and cycloalkoxy;

R<sup>2</sup> is selected from the group consisting of hydrogen, alkoxy, alkycycloalkoxy, cycloalkoxy and halogen, or when R<sup>1</sup> and R<sup>2</sup> are attached to adjacent carbon atoms, R<sup>1</sup> and R<sup>2</sup> may be joined together to form an alkylenedioxy group;

R<sup>3</sup> is selected from the group consisting of hydrogen, alkoxy, alkycycloalkoxy, cycloalkoxy and halogen;

R<sup>4</sup> is selected from the group consisting of hydrogen and alkyl;

R<sup>5</sup> is selected from the group consisting of alkyl having at least 3 carbon atoms, substituted alkyl having at least 3 carbon atoms and cycloalkyl;

provided that:

(i) when R<sup>2</sup> and R<sup>3</sup> are independently hydrogen or methoxy, R<sup>1</sup> is not methoxy;

(ii) when R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are hydrogen and R<sup>5</sup> is *tert*-butyl, then R<sup>1</sup> is not 4-*n*-butoxy, 4-*n*-pentyloxy or 4-*n*-hexyloxy;

(iii) when R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are hydrogen and R<sup>5</sup> is isopropyl, then R<sup>1</sup> is not 4-ethoxy;

(iv) when R<sup>1</sup> and R<sup>2</sup> are joined together to form a 3,4-methylenedioxy group and R<sup>3</sup> and R<sup>4</sup> are hydrogen, then R<sup>5</sup> is not isopropyl or *tert*-butyl;

(v) when R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are hydrogen and R<sup>5</sup> is 1-hydroxy-2-methylprop-2-yl, then R<sup>1</sup> is not 2-ethoxy;

(vi) when R<sup>1</sup> is 4-methoxy, R<sup>2</sup> is 3-ethoxy, and R<sup>3</sup> and R<sup>4</sup> are hydrogen, then R<sup>5</sup> is not 2,2-dimethylbut-3-yl or 1-hydroxy-2-methylprop-2-yl; and

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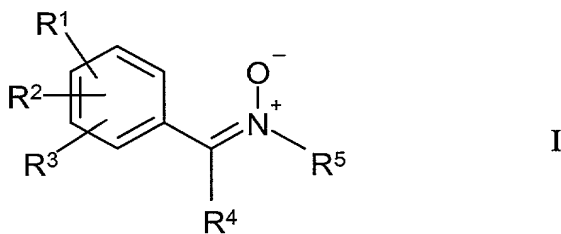
(vii) when R<sup>3</sup> and R<sup>4</sup> are hydrogen and R<sup>5</sup> is *tert*-butyl, then R<sup>1</sup> is not 4-methoxy when R<sup>2</sup> is 2-fluoro, and R<sup>1</sup> is not 2-methoxy when R<sup>2</sup> is 4-fluoro.

46. The method according to Claim 45 wherein the neurodegenerative disease is Alzheimer's disease.

47. The method according to Claim 45 wherein the neurodegenerative disease is Parkinson's disease.

48. The method according to Claim 45 wherein the neurodegenerative disease is HIV dementia.

50. A method for ameliorating a cause of an autoimmune disease in a patient at risk for developing the autoimmune disease which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective autoimmune disease-cause-ameliorating amount of a compound of formula I:



wherein

R<sup>1</sup> is selected from the group consisting of alkoxy, alkaryloxy, alkycycloalkoxy, aryloxy, and cycloalkoxy;

R<sup>2</sup> is selected from the group consisting of hydrogen, alkoxy, alkycycloalkoxy, cycloalkoxy and halogen, or when R<sup>1</sup> and R<sup>2</sup> are attached to adjacent carbon atoms, R<sup>1</sup> and R<sup>2</sup> may be joined together to form an alkylenedioxy group;

R<sup>3</sup> is selected from the group consisting of hydrogen, alkoxy, alkycycloalkoxy, cycloalkoxy and halogen;

R<sup>4</sup> is selected from the group consisting of hydrogen and alkyl;

R<sup>5</sup> is selected from the group consisting of alkyl having at least 3 carbon atoms, substituted alkyl having at least 3 carbon atoms and cycloalkyl;

provided that:

(i) when R<sup>2</sup> and R<sup>3</sup> are independently hydrogen or methoxy, R<sup>1</sup> is not methoxy;

(ii) when R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are hydrogen and R<sup>5</sup> is *tert*-butyl, then R<sup>1</sup> is not 4-*n*-butoxy, 4-*n*-pentyloxy or 4-*n*-hexyloxy;

(iii) when R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are hydrogen and R<sup>5</sup> is isopropyl, then R<sup>1</sup> is not 4-ethoxy;

(iv) when R<sup>1</sup> and R<sup>2</sup> are joined together to form a 3,4-methylenedioxy group and R<sup>3</sup> and R<sup>4</sup> are hydrogen, then R<sup>5</sup> is not isopropyl or *tert*-butyl;

(v) when R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are hydrogen and R<sup>5</sup> is 1-hydroxy-2-methylprop-2-yl, then R<sup>1</sup> is not 2-ethoxy;

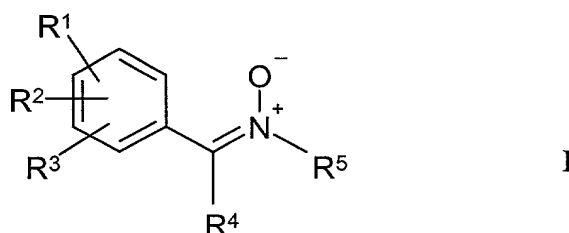
(vi) when R<sup>1</sup> is 4-methoxy, R<sup>2</sup> is 3-ethoxy, and R<sup>3</sup> and R<sup>4</sup> are hydrogen, then R<sup>5</sup> is not 2,2-dimethylbut-3-yl or 1-hydroxy-2-methylprop-2-yl; and

(vii) when R<sup>3</sup> and R<sup>4</sup> are hydrogen and R<sup>5</sup> is *tert*-butyl, then R<sup>1</sup> is not 4-methoxy when R<sup>2</sup> is 2-fluoro, and R<sup>1</sup> is not 2-methoxy when R<sup>2</sup> is 4-fluoro.

51. The method according to Claim 50 wherein the autoimmune disease is systemic lupus.

52. The method according to Claim 50 wherein the autoimmune disease is multiple sclerosis.

54. A method for ameliorating a cause of an inflammatory disease in a patient at risk for developing the inflammatory disease which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective inflammatory disease-cause=ameliorating amount of a compound of formula I:



wherein

$R^1$  is selected from the group consisting of alkoxy, alkaryloxy, alkycycloalkoxy, aryloxy, and cycloalkoxy;

$R^2$  is selected from the group consisting of hydrogen, alkoxy, alkycycloalkoxy, cycloalkoxy and halogen, or when  $R^1$  and  $R^2$  are attached to adjacent carbon atoms,  $R^1$  and  $R^2$  may be joined together to form an alkylenedioxy group;

$R^3$  is selected from the group consisting of hydrogen, alkoxy, alkycycloalkoxy, cycloalkoxy and halogen;

$R^4$  is selected from the group consisting of hydrogen and alkyl;

$R^5$  is selected from the group consisting of alkyl having at least 3 carbon atoms, substituted alkyl having at least 3 carbon atoms and cycloalkyl;

provided that:

(i) when  $R^2$  and  $R^3$  are independently hydrogen or methoxy,  $R^1$  is not methoxy;

(ii) when  $R^2$ ,  $R^3$  and  $R^4$  are hydrogen and  $R^5$  is *tert*-butyl, then  $R^1$  is not 4-*n*-butoxy, 4-*n*-pentyloxy or 4-*n*-hexyloxy;

(iii) when  $R^2$ ,  $R^3$  and  $R^4$  are hydrogen and  $R^5$  is isopropyl, then  $R^1$  is not 4-ethoxy;

(iv) when  $R^1$  and  $R^2$  are joined together to form a 3,4-methylenedioxy group and  $R^3$  and  $R^4$  are hydrogen, then  $R^5$  is not isopropyl or *tert*-butyl;

(v) when  $R^2$ ,  $R^3$  and  $R^4$  are hydrogen and  $R^5$  is 1-hydroxy-2-methylprop-2-yl, then  $R^1$  is not 2-ethoxy;

(vi) when  $R^1$  is 4-methoxy,  $R^2$  is 3-ethoxy, and  $R^3$  and  $R^4$  are hydrogen, then  $R^5$  is not 2,2-dimethylbut-3-yl or 1-hydroxy-2-methylprop-2-yl; and

(vii) when  $R^3$  and  $R^4$  are hydrogen and  $R^5$  is *tert*-butyl, then  $R^1$  is not 4-methoxy when  $R^2$  is 2-fluoro, and  $R^1$  is not 2-methoxy when  $R^2$  is 4-fluoro.

55. The method according to Claim 54 wherein the inflammatory disease is rheumatoid arthritis.

56. The method according to Claim 54 wherein the inflammatory disease is septic shock.

57. The method according to Claim 54 wherein the inflammatory disease is erythema nodosum leprosy.

58. The method according to Claim 54 wherein the inflammatory disease is septicemia.

59. The method according to Claim 54 wherein the inflammatory disease is uveitis.

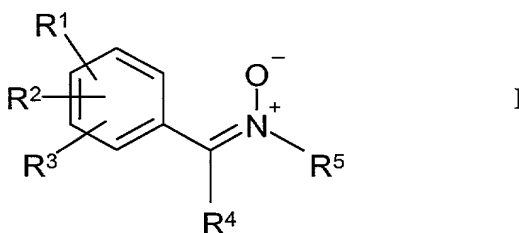
60. The method according to Claim 54 wherein the inflammatory disease is adult respiratory distress syndrome.

61. The method according to Claim 54 wherein the inflammatory disease is inflammatory bowel disease.

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## CLAIMS MARKED TO SHOW AMENDMENTS

45. (Amended) A method for ameliorating a cause [preventing the onset] of a neurodegenerative disease in a patient at risk for developing the neurodegenerative disease which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective neurodegenerative disease-casue- ameliorating [preventing] amount of a compound of formula I:



wherein

R<sup>1</sup> is selected from the group consisting of alkoxy, alkaryloxy, alkycycloalkoxy, aryloxy, and cycloalkoxy;

R<sup>2</sup> is selected from the group consisting of hydrogen, alkoxy, alkycycloalkoxy, cycloalkoxy and halogen, or when R<sup>1</sup> and R<sup>2</sup> are attached to adjacent carbon atoms, R<sup>1</sup> and R<sup>2</sup> may be joined together to form an alkylenedioxy group;

R<sup>3</sup> is selected from the group consisting of hydrogen, alkoxy, alkycycloalkoxy, cycloalkoxy and halogen;

R<sup>4</sup> is selected from the group consisting of hydrogen and alkyl;

R<sup>5</sup> is selected from the group consisting of alkyl having at least 3 carbon atoms, substituted alkyl having at least 3 carbon atoms and cycloalkyl;

provided that:

(i) when R<sup>2</sup> and R<sup>3</sup> are independently hydrogen or methoxy, R<sup>1</sup> is not methoxy;

(ii) when R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are hydrogen and R<sup>5</sup> is *tert*-butyl, then R<sup>1</sup> is not 4-*n*-butoxy, 4-*n*-pentyloxy or 4-*n*-hexyloxy;

(iii) when R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are hydrogen and R<sup>5</sup> is isopropyl, then R<sup>1</sup> is not 4-ethoxy;

(iv) when  $R^1$  and  $R^2$  are joined together to form a 3,4-methylenedioxy group and  $R^3$  and  $R^4$  are hydrogen, then  $R^5$  is not isopropyl or *tert*-butyl;

(v) when  $R^2$ ,  $R^3$  and  $R^4$  are hydrogen and  $R^5$  is 1-hydroxy-2-methylprop-2-yl, then  $R^1$  is not 2-ethoxy;

(vi) when  $R^1$  is 4-methoxy,  $R^2$  is 3-ethoxy, and  $R^3$  and  $R^4$  are hydrogen, then  $R^5$  is not 2,2-dimethylbut-3-yl or 1-hydroxy-2-methylprop-2-yl; and

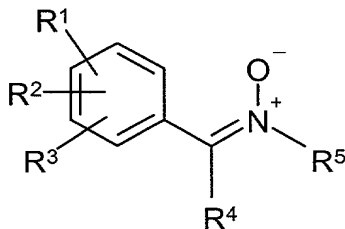
(vii) when  $R^3$  and  $R^4$  are hydrogen and  $R^5$  is *tert*-butyl, then  $R^1$  is not 4-methoxy when  $R^2$  is 2-fluoro, and  $R^1$  is not 2-methoxy when  $R^2$  is 4-fluoro.

46. (Amended) The method according to Claim [44 or] 45 wherein the neurodegenerative disease is Alzheimer's disease.

47. (Amended) The method according to Claim [44 or] 45 wherein the neurodegenerative disease is Parkinson's disease.

48. (Amended) The method according to Claim [44 or] 45 wherein the neurodegenerative disease is HIV dementia.

50. (Amended) A method for ameliorating a cause [preventing the onset] of an autoimmune disease in a patient at risk for developing the autoimmune disease which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective autoimmune disease cause-ameliorating [preventing] amount of a compound of formula I:



I

wherein

R<sup>1</sup> is selected from the group consisting of alkoxy, alkaryloxy, alkycycloalkoxy, aryloxy, and cycloalkoxy;

R<sup>2</sup> is selected from the group consisting of hydrogen, alkoxy, alkycycloalkoxy, cycloalkoxy and halogen, or when R<sup>1</sup> and R<sup>2</sup> are attached to adjacent carbon atoms, R<sup>1</sup> and R<sup>2</sup> may be joined together to form an alkylenedioxy group;

R<sup>3</sup> is selected from the group consisting of hydrogen, alkoxy, alkycycloalkoxy, cycloalkoxy and halogen;

R<sup>4</sup> is selected from the group consisting of hydrogen and alkyl;

R<sup>5</sup> is selected from the group consisting of alkyl having at least 3 carbon atoms, substituted alkyl having at least 3 carbon atoms and cycloalkyl;

provided that:

(i) when R<sup>2</sup> and R<sup>3</sup> are independently hydrogen or methoxy, R<sup>1</sup> is not methoxy;

(ii) when R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are hydrogen and R<sup>5</sup> is *tert*-butyl, then R<sup>1</sup> is not 4-*n*-butoxy, 4-*n*-pentyloxy or 4-*n*-hexyloxy;

(iii) when R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are hydrogen and R<sup>5</sup> is isopropyl, then R<sup>1</sup> is not 4-ethoxy;

(iv) when R<sup>1</sup> and R<sup>2</sup> are joined together to form a 3,4-methylenedioxy group and R<sup>3</sup> and R<sup>4</sup> are hydrogen, then R<sup>5</sup> is not isopropyl or *tert*-butyl;

(v) when R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are hydrogen and R<sup>5</sup> is 1-hydroxy-2-methylprop-2-yl, then R<sup>1</sup> is not 2-ethoxy;

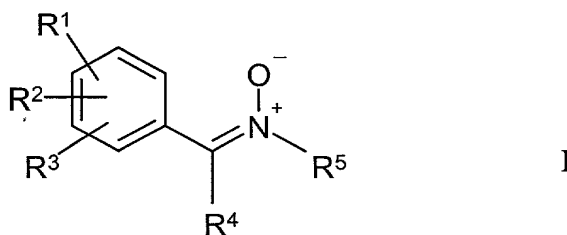
(vi) when R<sup>1</sup> is 4-methoxy, R<sup>2</sup> is 3-ethoxy, and R<sup>3</sup> and R<sup>4</sup> are hydrogen, then R<sup>5</sup> is not 2,2-dimethylbut-3-yl or 1-hydroxy-2-methylprop-2-yl; and

(vii) when R<sup>3</sup> and R<sup>4</sup> are hydrogen and R<sup>5</sup> is *tert*-butyl, then R<sup>1</sup> is not 4-methoxy when R<sup>2</sup> is 2-fluoro, and R<sup>1</sup> is not 2-methoxy when R<sup>2</sup> is 4-fluoro.

51. (Amended) The method according to Claim [49 or] 50 wherein the autoimmune disease is systemic lupus.

52. (Amended) The method according to Claim [49 or] 50 wherein the autoimmune disease is multiple sclerosis.

54. (Amended) A method for ameliorating a cause [preventing the onset] of an inflammatory disease in a patient at risk for developing the inflammatory disease which method comprises administering to said patient a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an effective inflammatory disease-cause-ameliorating [preventing] amount of a compound of formula I:



wherein

R<sup>1</sup> is selected from the group consisting of alkoxy, alkaryloxy, alkycycloalkoxy, aryloxy, and cycloalkoxy;

R<sup>2</sup> is selected from the group consisting of hydrogen, alkoxy, alkycycloalkoxy, cycloalkoxy and halogen, or when R<sup>1</sup> and R<sup>2</sup> are attached to adjacent carbon atoms, R<sup>1</sup> and R<sup>2</sup> may be joined together to form an alkylenedioxy group;

R<sup>3</sup> is selected from the group consisting of hydrogen, alkoxy, alkycycloalkoxy, cycloalkoxy and halogen;

R<sup>4</sup> is selected from the group consisting of hydrogen and alkyl;

R<sup>5</sup> is selected from the group consisting of alkyl having at least 3 carbon atoms, substituted alkyl having at least 3 carbon atoms and cycloalkyl;

provided that:

- (i) when R<sup>2</sup> and R<sup>3</sup> are independently hydrogen or methoxy, R<sup>1</sup> is not methoxy;
- (ii) when R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are hydrogen and R<sup>5</sup> is *tert*-butyl, then R<sup>1</sup> is not 4-*n*-butoxy, 4-*n*-pentyloxy or 4-*n*-hexyloxy;
- (iii) when R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are hydrogen and R<sup>5</sup> is isopropyl, then R<sup>1</sup> is not 4-ethoxy;

(iv) when R<sup>1</sup> and R<sup>2</sup> are joined together to form a 3,4-methylenedioxy group and R<sup>3</sup> and R<sup>4</sup> are hydrogen, then R<sup>5</sup> is not isopropyl or *tert*-butyl;

(v) when R<sup>2</sup>, R<sup>3</sup> and R<sup>4</sup> are hydrogen and R<sup>5</sup> is 1-hydroxy-2-methylprop-2-yl, then R<sup>1</sup> is not 2-ethoxy;

(vi) when R<sup>1</sup> is 4-methoxy, R<sup>2</sup> is 3-ethoxy, and R<sup>3</sup> and R<sup>4</sup> are hydrogen, then R<sup>5</sup> is not 2,2-dimethylbut-3-yl or 1-hydroxy-2-methylprop-2-yl; and

(vii) when R<sup>3</sup> and R<sup>4</sup> are hydrogen and R<sup>5</sup> is *tert*-butyl, then R<sup>1</sup> is not 4-methoxy when R<sup>2</sup> is 2-fluoro, and R<sup>1</sup> is not 2-methoxy when R<sup>2</sup> is 4-fluoro.

55. (Amended) The method according to Claim [53 or] 54 wherein the inflammatory disease is rheumatoid arthritis.

56. (Amended) The method according to Claim [53 or] 54 wherein the inflammatory disease is septic shock.

57. (Amended) The method according to Claim [53 or] 54 wherein the inflammatory disease is erythema nodosum leprosy.

58. (Amended) The method according to Claim [53 or] 54 wherein the inflammatory disease is septicemia.

59. (Amended) The method according to Claim [53 or] 54 wherein the inflammatory disease is uveitis.

60. (Amended) The method according to Claim [53 or] 54 wherein the inflammatory disease is adult respiratory distress syndrome.

61. (Amended) The method according to Claim [53 or] 54 wherein the inflammatory disease is inflammatory bowel disease.

**R E M A R K S**

Applicants respectfully request that the above amendments be entered prior to examination of this application on the merits and that the claims in this application be allowed.

Claims 1-44, 49, and 53 are being canceled. Accordingly, Claims 45-48, 50-52 and 54-61 are now pending in this application.

1. Summary of the Amendments

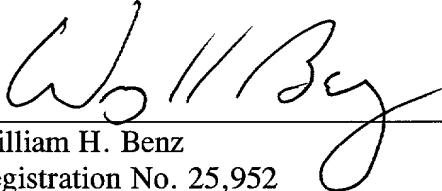
Claim 1-44, 49 and 53 have been canceled since these claims were previously allowed in the grandparent application, U.S. Serial No. 09/172,763. Additionally, Claims 46-48, 51, 52, 55-61 have been amended to delete their dependency on now canceled claims.

All of the claims have been amended to reite that they relate to "ameliorating a cause of a disease" rather than to "preventing the disease". The Examples in this application depict a number of settings in which a cause of a disease is ameliorated to the extent that evidence of the causes action is not detected.

Entry of these amendments and examination of this application on the merits is respectfully requested.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By:   
William H. Benz  
Registration No. 25,952

P.O. Box 1404  
Alexandria, Virginia 22313-1404  
(650) 622-2300

Date: February 11, 2002

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